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TITLE: A Randomized, Controlled Trial of Intranasal Oxytocin as an Adjunct to Behavioral Therapy for Autism Spectrum Disorder

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14. ABSTRACT The primary objectives of this clinical study are test the two hypotheses that (1) cognitive behavioral therapy (CBT) aimed at core social dysfunctions and (2) oxytocin (OT) administration prior to CBT sessions will each enhance social function in young adults with autism spectrum disorders (ASD). A third objective is to examine whether neuroimaging measures of brain function and structure can predict CBT treatment responsiveness.					
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Section I: Purpose and scope of the research study

The primary objectives of this clinical study are test the two hypotheses that (1) cognitive behavioral therapy (CBT) aimed at core social dysfunctions and (2) oxytocin (OT) administration prior to CBT sessions will each enhance social function in young adults with autism spectrum disorders (ASD). A third objective is to examine whether neuroimaging measures of brain function and structure can predict CBT treatment responsiveness.

Specific Aim 1 – Recruit and Clinically Characterize 150 Males Ages 18-30 with ASD

Through multiple local clinical and research relations of the investigators, we will recruit and carefully characterize 150 men, ages 18-30, with ASD to participate in this study. These will all be high-functioning patients with IQ scores in the average-to-above average range (90 and higher). We anticipate that about 16% of volunteers will drop out of study, leaving the 43 volunteers per group that power analyses indicate will reveal moderate or greater effects of CBT or OT. We examine males only because of the preponderance of males with ASD and the interactions between OT and sex would require a very large number of participants to be adequately statistically powered.

Specific Aim 2 - Random, Stratified Assignment to Three Groups in a Double-Blind, Placebo Controlled Clinical Trial Design

We will randomly assign ASD volunteers into three 50-person groups, with stratification (equation) on age, ASD severity (ADOS score), and non-verbal IQ so that the three groups are equated on those important dimensions. The three groups are:

- (1) Group 1 (*All Placebo*), who will receive an active placebo behavioral treatment of 12 sessions of relaxation training, and placebo medication;
- (2) Group 2 (*CBT/placebo*), who will receive the experimental CBT 12-session treatment, and placebo medication; and
- (3) Group 3 (*CBT/OT*), who will receive the experimental treatment, and OT before 12 sessions of CBT treatment.

Volunteers (patients) and evaluators will be blind to condition assignment (double-blind design). We will test the *hypothesis* that CBT helps ASD adults by statistically comparing Groups 1 and 2 on outcome measures (the inclusion of medication placebo equates expectancy effects across the two groups). We will test the *hypothesis* that OT enhances CBT effectiveness in ASD adults by statistically comparing Groups 2 and 3 on outcome measures.

Specific Aim 3 – Use of Neuroimaging to Predict Response to Treatment

We will perform functional (fMRI) and structural (MRI) imaging with all participants prior to treatment. We will examine statistically, for each group, the relations between measures of brain function and structure with improvements on outcome measures to discover whether there are neural characteristics that

can identify which ASD patients are most likely to respond to behavioral intervention.

Section II. Progress To-Date (As per Statement of Work)

Task 1. IRB approval

Submit clinical trial description documents to local IRBs and HRPO.

1a. Update consent forms to reflect local IRB and HRPO regulations (months 1) MIT+MGH

1b. Apply for MIT IRB approval (months 1-3) MIT

- **We initially submitted the application for IRB approval in May 2013, initial submission was given in October 2013.**
- **Final approval is pending HRPO approval.**

1c. Apply for MGH IRB approval (months 1-3) MGH

1d. Apply United States Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO) approval (months 2-5) MGH+MIT

- **We received an IND from the FDA for the use of oxytocin in the study**
- **We submitted the protocol to the MGH IRB in May 2013 and received approval in October 2013**
- **We submitted the protocol to the HRPO upon preliminary approval from MGH and MIT IRB. Final approval from the HRPO is pending.**
- **We have created a CT.gov account for the study**
- **Both MIT and MGH sites are in the application process to get access to NDAR (National Database for Autism Research).**

Task 2. Staff recruitment and preparation of testing materials, initial pilot study

This task involves setting up the system for subject recruitment, randomization and tracking. As well as setting up a system for continuously adding assessment results.

- **We completed all of the hiring of study staff. The study staff is as follows:**
 - **Dina Hirshfeld-Becker, Ph.D. (independent evaluator at MGH)**
 - **Noah Berman, Ph.D. (independent evaluator at MGH)**
 - **Margaret Kjølgaard, Ph.D. (ADOS and ADI-R evaluator at MGH/MIT)**
 - **Angela Utschig, Ph.D. (study therapist at MGH)**
 - **Jamie Micco, Ph.D. (study therapist at MGH)**
 - **Gagan Joshi, MD (study physician)**
 - **Janet Wozniak, MD (study physician)**

- **Satrajit Gosh, Ph.D. (neuroimager and statistician, MIT)**
- **Dorit Kliemann, Dr. (neuroimager and project coordinator at MIT)**
- **Melissa Schoeller (research assistant)**
- **Lexi Boudreaux (research assistant)**
- **We have trained study clinicians on the CBT therapy protocol, and the independent evaluators on the study measures**
- **We have initiated regular meeting with MIT and MGH staff to jointly coordinate ongoing steps and topics.**
- **We have been entering questionnaires into RedCap, an MGH-supported electronic data capture system that will allow us to administer the study questionnaires electronically rather than via paper-and-pencil**
- **MIT and MGH staff have been working to develop a data entry system that will facilitate cross-site sharing of data**

2a. Prepare stimuli and scanner protocol (months 1-3) MIT

We will create a setup for stimulus presentation using the Psychophysics Toolbox for MATLAB. The setup will include stimulus presentation for functional localizers used in the imaging sessions as well as tests for attention during the pre and post periods. Prepare stimuli and presentation for RMET and Social cooperation task.

- **Sequences for functional and structural neuroimaging prior to treatment have been tested for study eligibility (all with whole-brain coverage in a higher resolution 32-channel coil):**
 - ***Resting State:* 2x2x2 mm, TR=1.09s, TE=30 (2x- PA and AP phaseencoding)**
 - ***Structural:* MEMPRAGE: 1x1x1mm, Multi-echo (withpossiblemotioncorrection)**
 - ***T2 SPACE:* 1x1x1mm, bandwidthmatchedto T1-weighted MEMPRAGE**
 - ***Diffusion weighted:* 5mXXs, 2x2x2 mm, 61 directions, b=1000, 9 b=0 values (2x, PA, AP)**
 - ***Functionaltasks:* 3x3x3mm TR=2.5s, TE=30ms**
- **Pilot testing of functional tasks in the scanner has been started and is still ongoing to increase design and thus power efficienncy**

2b. Setup software for behavioral testing (months 1-3) MGH+MIT

The research coordinator will install the study software on the study purchased laptops.

- **We have identified several behavioral tasks and have been working with the developers of these tasks to ensure their usability and validity with our sample and our study design**

2c. Run pilot experiments (months 5-7) MGH+MIT

Run the initial pilot study to ensure all components are operational.

2d. Setup contract with pharmacy to supply drug and placebo after IRB approval.

- **We have been working with the MGH pharmacy, MGH mailroom, and the oxytocin distributor to obtain the oxytocin and placebo for the study. All procedures are in place, and we are ready to order the oxytocin/placebo upon HRPO approval of the protocol.**

Task 3. Begin recruitment of 150 subjects (Specific Aim 1,2)

We will start recruiting subjects for the study in an ongoing basis, taking care to balance enrollment subject to characterization by clinical assessment.

3a. Announce study to clinics, referral sources (months 5-34) MGH

- **We have created advertising materials including clinician and patient letters, advertisements to be posted on the subway and other public locations, and internet advertisements (these will be posted upon receiving HRPO approval)**
- **We have been meeting with local individuals and agencies (e.g., Lurie center, Child Psychiatry Department, and Bressler center) to inform them of our study and facilitate recruitment.**

Task 4. Subject workflow (months 5-34)

After consenting, all subjects will undergo characterization by the clinician and if admitted to the study will be scheduled for imaging sessions and will be given directives on how to use the software.

4a. Telephone screen MGH

- **We have developed the telephone screen and received MGH IRB Approval for its use. Study screening is not yet initiated.**

4b. Characterization by clinician (Specific Aim 1) The characterization of subjects will include a formal clinical neurological examination and symptom assessment as described in Specific Aim 1, and a neuroimaging exam (Specific Aim 3). MGH + MIT

- **As noted above, we have been training the independent evaluators in the study measures. Study characterization is not yet initiated.**

4c. Schedule imaging session. MIT
- **Not yet initiated**

4d. Schedule CBT. MGH
- **Not yet initiated**

Task 5. Perform neuroimaging, pre-treatment assessment and CBT(Specific Aim 2, 3; months 5-34) MGH + MIT
During this phase all subject data are collected. Each subject participates in the study for approximately 60 days.

5a. Collect imaging data during pre-treatment visit. MIT
Visit 1 (pre-treatment) consist of structural and functional brain measures requiring 1 hour in the scanner per visit. Diffusion, structural and functional data will be collected.
- **Not yet initiated**

5b. Perform CBT for 12 weeks (12 sessions) MGH
- **Not yet initiated**

5c. Safety Review
Data collected for the proposed research will be stored in secure physical files, and password protected electronic files. All measures will be taken to protect the identity of participants. The files from this study may be available for review by USAMRAA, the Institutional Review Board (IRB) at MIT and MGH, and by representatives of other governmental agencies as part of their normal duties. All records will be kept in a confidential form. Otherwise, only the members of the research team conducting this study will have access to the study records. Information gained from this study may be used as part of a scientific publication, however, participants will in no way be personally identified. We will keep completely de-identified data wherever possible so that sharing of data is easiest and available for submission into the NDAR.
- **Not yet initiated**

Task 6. Analysis of data (Specific Aim 2,3; months 5-34) MIT + MGH
The data will be analyzed at both MIT and MGH. The focus at MIT will be on the analysis of the imaging data, while the focus at MGH will be to analyze the clinical assessment data.
- **Not yet initiated**

6a. Analysis of imaging data
The imaging data will be analyzed using the NiPyPE imaging analysis framework using tools from well established neuroimaging analysis packages (SPM, FSL and FreeSurfer).
- **Not yet initiated**

6b. Analysis of behavioral data

When each participant completes the study, the research coordinator will download the participants data from the secure web portal. Research coordinator will transcribe these data into the centralized study database for statistical analysis as described in the full research proposal.

- Not yet initiated

Task 7. Preparation and publication of results (Specific Aim 3,4; months 34-36)
Once sufficient data has been prediction models will be prepared in order to determine which form of treatment is most effective for a particular case characterization.

7a. Preparation of treatment prediction models MIT

7b. Preparation of manuscripts MIT+MGH

7c. Submission of curated data into NDAR.

- Not yet initiated

List of acronyms

DTI – Diffusion tensor imaging

fMRI – Functional magnetic resonance imaging

MGH – Massachusetts General Hospital

MIT - Massachusetts Institute of Technology

RCT – Randomized control trial

Section III - Problem Areas

We initially dealt with a 3-month delay in the project funding and project start because of administrative issues as the primary project site was moved from MIT to MGH (Initial Project Start Date was October 1, 2012; funding not received until mid-December 2012 so actual start date is January 1, 2013). We also encountered several delays in the human subjects' approval process so that MGH/MIT IRB approval took nearly six months. There were additional delays in the approval process associated with the government shutdown in the fall of 2013. Because of these factors, we are still awaiting final approval of our study protocol, which means that we have not been able to initiate study procedures. Nevertheless, we have been using the time to refine our study procedures and set up all the necessary study components so that we will be able to quickly initiate the study once approval is received.

Section IV - Work to be Performed During the Next Reporting Period

During the next reporting period, we will achieve the following goals:

- conduct weekly staff meetings with various staff to review study progress,

- discuss clinical issues, and avoid rater/clinician drift
- upon approval from DOD, initiate study recruitment and begin to enroll study participants
- implement baseline assessment and neuroimaging protocols

Section V - Administrative Comments

None